Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5265–5272

TETRAHEDRON

A convenient approach to the synthesis of 2-(2-aminoethyl)pyrroles and their heterocyclization into hydrogenated pyrrolopyridines and related pyrroloindolizines

Marina V. Raiman,[a] Aleksei V. Pukin,[a] Vladimir I. Tyvorskii,[a] Norbert De Kimpe[b] and Oleg G. Kulinkovich[a,*]

[a]*Department of Organic Chemistry, Belarusian State University, Fr. Scorina Avenue, 4, 220050 Minsk, Belarus*
[b]*Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium*

Received 17 January 2003; revised 15 April 2003; accepted 16 May 2003

Abstract—2-(2-Aminoethyl)pyrroles and 2-(2-succinimidoethyl)pyrroles were prepared from acetals of ethyl 4-oxoalkanoates via latent vinyl 1,4-dicarbonyl compounds as the key intermediates. The Pictet–Spengler condensation of 2-(2-aminoethyl)pyrroles with aromatic aldehydes gave 4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridines in good yields. 4,5,7,8,9,9a-Hexahydro-3*H*-pyrrolo[2,3-*g*]indolizines were prepared in a similar way starting from 2-(2-succinimidoethyl)pyrroles.

1. Introduction

Pyrrolopyridines with different types of ring fusions and their partially hydrogenated derivatives are of great interest as aza-analogues of indole.[1] Methods for the synthesis of 4,5,6,7-tetrahydropyrrolo[3,2-*c*]pyridines, which show interesting biological activity and which have found application as synthetic building blocks, were summarized in a recent review.[2] The most important of them are based on the pyrrole annelation onto the corresponding piperidin-4-one framework, as well as on the formation of a hydrogenated pyridine ring by means of cyclisation of 2-(2-aminoethyl)pyrroles.[3,4] The latter approach appeared to be effective in the synthesis of previously unknown octahydropyridopyrrolopyridines in the acid-catalysed Pictet–Spengler reaction.[5] Similar non-catalytic heterocyclisations have been also accomplished in the series of tryptamine derivatives and have preparative importance for acidophobic pyrrole and indole systems.[6,7]

In the present work a convenient approach to the synthesis of 2-(2-aminoethyl)pyrroles **7a–c** and their succinimide analogues **7d–f**, starting from carbonyl-protected esters of γ-oxocarboxylic acids **1a**,**b**, is demonstrated (Schemes 1 and 2). The key precursors of compounds **7** were β-bromoketones **4**, **5** prepared by cyclopropanation of esters **1** with ethylmagnesium bromide in the presence of titanium(IV) isopropoxide[8] followed by brominative ring opening of the three-membered ring in cyclopropanols **2a**,**b**.[9] Compounds **7a–c** were smoothly converted into 4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridines **10a–i** by reaction with aromatic aldehydes in *i*-PrOH (Scheme 3). The related tricyclic compounds **13a–c**, bearing the pharmacophoric indolizine fragment were accessible similarly from compounds **7d–f** (Scheme 4).[10] Herein we describe our results.

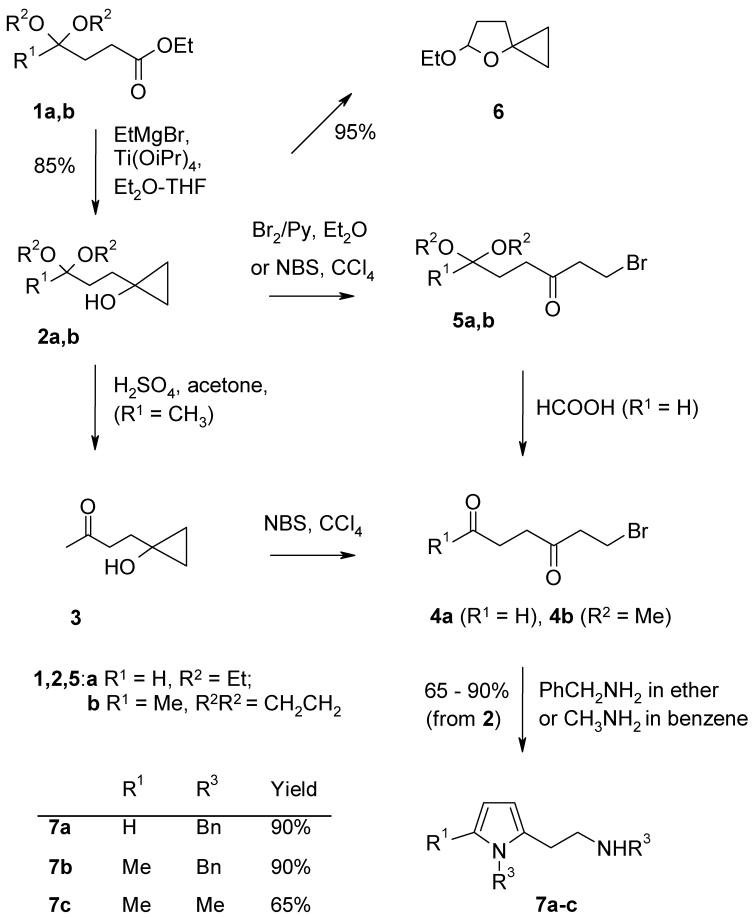
2. Results and discussion

6-Bromo-4-oxohexanal **4a** was obtained in three preparative steps in an overall yield of 67% starting from ethyl 4,4-diethoxybutanoate **1a** via the cyclopropanol intermediate **2a** as a key product (Scheme 1). Deprotection of aldehyde group was performed after bromination of the substituted cyclopropanol **2a**, since hydrolysis of the latter led to the formation of the cyclic acetal **6**[11] which was stable under bromination conditions. In contrast, deprotection of the ketone group in cyclopropanol derivative **2b** proceeded with formation of monocyclic acetonylmethylcyclopropanol **3**,[8e] and bromination of the latter led to 7-bromoheptan-2,5-dione **4b** in good yield (Scheme 1). The resulting β-bromoketones **4a**,**b** and **5a**,**b** were not stable and readily lost hydrogen bromide, merely upon contact with a adsorbent for chromatography. Therefore, these compounds were used for further transformations without purification (purity >98%; ^{1}H NMR spectroscopy).

Keywords: cyclopropanols; 2-aminoethylpyrroles; pyrrolopyridines; pyrroloindolizines; Pictet–Spengler reaction.

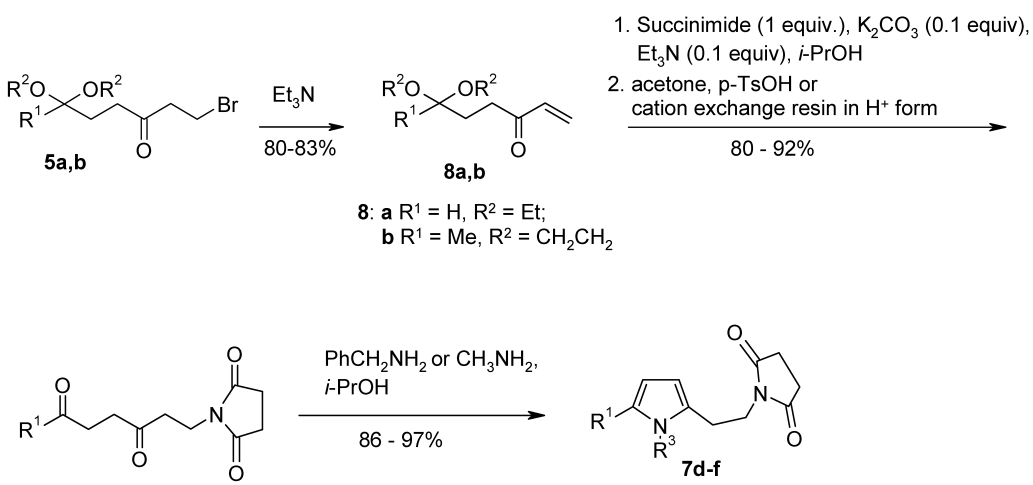
* Corresponding author. Tel.: +375-17-2095190; fax: +375-17-2265609; e-mail: kulinkovich@bsu.by

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00777-4



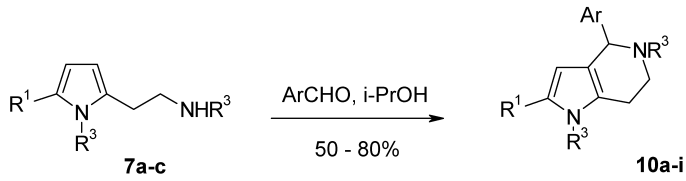
	R^1	R^3	Yield
7a	H	Bn	90%
7b	Me	Bn	90%
7c	Me	Me	65%

Scheme 1.



	R^1	R^3	Yield
7d	H	Bn	97%
7e	Me	Bn	86%
7f	Me	Me	91%

Scheme 2.



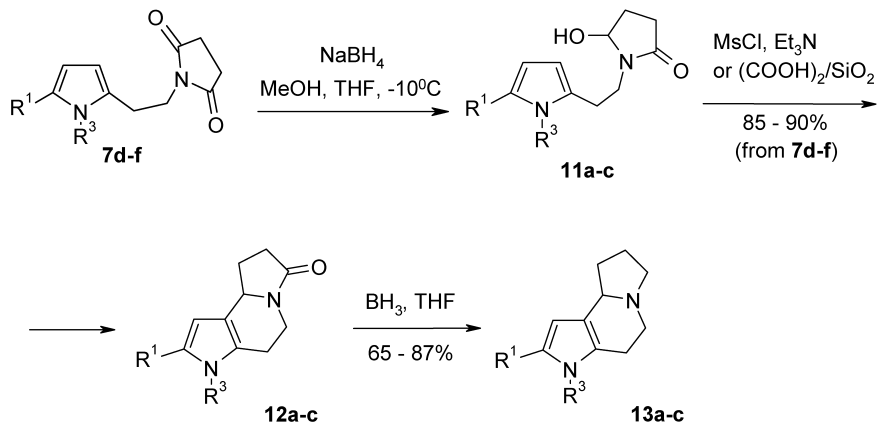
	R^1	R^3	Ar	Yield		R^1	R^3	Ar	Yield
10a	Me	Bn	Ph	80%	**10f**	Me	Me	Ph	50%
10b	Me	Bn	4-ClC_6H_4	78%	**10g**	Me	Me	3-$NO_2C_6H_4$	63%
10c	Me	Bn	4-FC_6H_4	65%	**10h**	H	Bn	Ph	77%
10d	Me	Bn	3-$NO_2C_6H_4$	75%	**10i**	H	Bn	4-ClC_6H_4	70%
10e	Me	Bn	2-OH-5-$NO_2C_6H_3$	63%					

Scheme 3.

7-Bromoheptan-2,5-dione **4b** and 6-bromo-4-oxohexanal **4a** reacted readily with three equivalents of benzylamine in diethyl ether at room temperature to produce pyrroles **7a**,**b** in high yields. The corresponding *N*-methyl compound **7c** was obtained in moderate yield upon bubbling of gaseous methylamine through an ethereal solution of 7-bromoheptan-2,5-dione **4b**.

2-(2-Succinimido)pyrroles **7d**–**f** were prepared in a similar way to that of compounds **7a**–**c** (Scheme 2). However, the use of β-bromoketones **4a**,**b** as precursors of pyrroles **7d**–**f** resulted only in moderate yields of the target products. Better results were achieved by preliminary transformation of the protected bromoketones **5a**,**b** into the corresponding vinyl ketones **8a**,**b** followed by reaction of the latter enones with equimolar quantities of succinimide and catalytic amounts of K_2CO_3 and triethylamine. The use of either of these catalysts separately, led to an extension of the reaction time which may be due to the non-sufficient solubility of potassium carbonate and deficient basicity of triethylamine. Combined use of these bases probably evoked phase transfer catalytic processes. To remove the acetal protecting group, the resulting crude product was treated with acetone in the presence of *p*-toluenesulfonic acid or cation exchange resin (in H^+-form). The use of the latter in the synthesis of **9a** allows simplification of the work-up procedure and an increase in the yield of the product. To obtain the pyrroles **7d**–**f**, the corresponding dicarbonyl compounds **9a**,**b** were involved in a heterocyclization reaction with benzylamine or methylamine.

N,*N*′-Dialkyl-2-(2-aminoethyl)pyrroles **7a**–**c** were converted into the target fused compounds **10a**–**i** by Pictet–Spengler condensation with aromatic aldehydes in *i*-PrOH (Scheme 3). The reaction was complete within 2–4 h at room temperature, and tetrahydropyrrolopyridines **10a**–**g** precipitated from the reaction mixture as crystalline products (80–90% yield after recrystallisation from *i*-PrOH). Pyrrolopyridines **10h**,**i** having no substituents at the α-position of the pyrrole ring, were obtained in similar manner at 0°C, and were isolated by column chromatography with somewhat lower yields. It should be noted that in contrast to the reported procedure,[5] a non-catalytic variant of the Pictet–Spengler reaction was used which allowed us to isolate acidophobic compounds **10h**,**i** as free bases in good yields.



11,12,13: **a** R^1 = H, R^3 = Bn;
b R^1 = Me, R^3 = Bn;
c R^1 = Me, R^3 = Me

	R^1	R^3	Yield
13a	H	Bn	87%
13b	Me	Bn	78%
13c	Me	Me	65%

Scheme 4.

2-(2-Succinimidoethyl)pyrroles **7d**–**f** were converted into the corresponding pyrroloindolizines **13a**–**c** by a modified Pictet–Spengler reaction in which the heterocyclization steps were achieved by the intramolecular electrophilic addition of *N*-acyliminium ion generated from the partially reduced succinimide fragment of compounds **11a**–**c** (Scheme 4). The latter were obtained in quantitative yields by treatment of pyrroles **7d**–**f** with sodium borohydride in a CH_3OH-THF mixture at −10°C.[12]

The formation of the hemiaminals **11a**–**c** was supported spectroscopically by the appearance of the characteristic multiplet of the methine proton at 4.86–4.98 ppm in the ^1H NMR spectra ($CDCl_3$). The hemiaminals **11b**,**c**, without purification, were cyclized upon reaction with mesyl chloride in dichloromethane in the presence of triethylamine to give tricyclic pyrrolopyridine derivatives **12b**,**c** in good yields, whereas the less substituted pyrrole **11a** turned into a resin-like product under these conditions. The conversion of hemiaminal **11a** into pyrroloindolizidine **12a** was successfully achieved by treatment with oxalic acid on silica in diethyl ether. The structure of compounds **12a**–**c** was confirmed by the ^1H NMR spectra ($CDCl_3$), which revealed a characteristic triplet of doublets at 2.86–3.06 ($J_{gem}\approx J_{aa}$=12.0 Hz; J_{ae}=5.5 Hz) for the axial 5-H proton and a doublet of doublets at 4.32–4.48 (J_{gem}=12.0 Hz; J_{ea}=5.5 Hz; J_{ee}=0 Hz) for the equatorial 5-H proton deshielded due to the anisotropic effect of the amide carbonyl.[13]

The amide moiety of compounds **12a**–**c** was reduced using 1 M borane in tetrahyrofuran,[14] and the resulting compounds **13a**–**c** were purified by column chromatography. The NMR spectra ($CDCl_3$) of the products **13a**–**c** showed an upfield shift of the equatorial 5-H proton signal (4.32–4.48 ppm in the spectra of **12a**–**c**).

In conclusion, an effective route to substituted 4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridines and related 4,5,7,8,9,9a-hexahydro-3*H*-pyrrolo[2,3-*g*]indolizines was developed, starting from acetals of ethyl 4-oxoalkanoates via the preparation of latent vinyl 1,4-dicarbonyl compounds as the key intermediates.

3. Experimental

3.1. General

IR spectra were measured on a Specord 75 IR spectrophotometer. ^1H NMR spectra were recorded at 60 MHz (Tesla BS-467) in CCl_4 with hexamethyldisiloxane as the internal standard, or 200 MHz (Bruker-200) with TMS as the internal standard, or 400 MHz (Bruker Avance 400) with $CDCl_3$ as the solvent. ^{13}C NMR spectra were recorded with a Bruker Avance 400 at 100.6 MHz with $CDCl_3$ as solvent. Melting points were determined in open capillaries and are uncorrected. Preparative column chromatography was carried out on silica gel (Merck; 70–230 Mesh). All chemicals were reagent grade; solvents were dried and distilled prior to use. The cation exchanger resin (in H^+-form) was obtained from the Reakhim Company.

The cyclopropanols **2b**, **3** were prepared according to the known procedures.[8e]

3.1.1. 1-(3,3-Diethoxypropyl)-1-cyclopropanol (2a). A solution of ethylmagnesium bromide in Et_2O (5 mL of 3.2 M solution, 16 mmol) was added to a stirred solution of ethyl 4,4-diethoxybutanoate **1a** (1 g, 4.9 mmol) and Ti(OPr-*i*)$_4$ (0.15 mL, 0.49 mmol) in dry Et_2O (10 mL) at room temperature over 10 min. The reaction mixture was stirred for 1 h and quenched with an ice-cold saturated aqueous solution of NH_4Cl (10 mL). After filtration, the organic layer was separated and the aqueous phase was extracted with Et_2O (3×3 mL). The organic phases were combined, washed with brine, dried with Na_2SO_4 and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (Et_2O–cyclohexane, 1:3) to give 0.78 g (85%) of cyclopropanol **2a** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 0.38–0.41 (m, 2H), 0.69–0.72 (m, 2H), 1.18 (t, *J*=7.2 Hz, 6H), 1.62 (t, *J*=7.2 Hz, 2H), 1.85 (dt, *J*=7.2, 5.1 Hz, 2H), 3.48 (dq, *J*=9.2, 7.2 Hz, 2H), 3.64 (dq, *J*=9.2, 7.2 Hz, 2H), 3.80 (bs, 1H), 4.56 (t, *J*=5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 13.5, 15.1, 30.5, 33.4, 55.0, 61.1, 102.9. Anal. calcd for $C_{10}H_{20}O_3$: C, 63.83; H, 10.64. Found: C, 63.88; H, 10.63.

3.1.2. 1-Benzyl-2-[2-(benzylamino)ethyl]pyrrole (7a). Bromine-pyridine complex (0.99 g, 4.15 mmol) was added portionwise to a stirred solution of cyclopropanol **2a** (0.78 g, 4.15 mmol) in dry Et_2O (10 mL) at 10°C over 10 min. The precipitate was removed by filtration and the solvent evaporated in vacuo to give the crude β-bromoketone **5a**. The latter was dissolved in 15 mL of acetone and 0.4 g of cation exchange resin in H^+-form was added. After stirring for 2 h the cation exchange resin was removed by filtration and the solvent was evaporated. The residue was dissolved in 15 mL of ether and the resulting solution of β-bromoketone **4a** was added dropwise to a vigorously stirred solution of benzylamine (1.36 mL, 12.45 mmol) in 15 mL of diethyl ether over 30 min. The precipitate was filtered, the solution washed with water, brine, filtered through a thick layer of alumina and dried over Na_2SO_4. Evaporation of the solvent followed by purification of the crude product on a column of silica (Et_2O–petroleum ether, 1:1) gave 0.92 g (76%) of β-(aminoethyl)pyrrole **7a** as a yellowish oil. IR ($CHCl_3$): ν_{max} 3346 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.54 (bs, 1H), 2.69 (t, *J*=7.2 Hz, 2H), 2.80 (t, *J*=7.2 Hz, 2H), 3.71 (s, 2H), 5.03 (s, 2H), 5.88–6.00 (m, 1H), 6.12–6.14 (m, 1H), 6.62–6.64 (m, 1H), 6.94–6.97 (m, 2H), 7.20–7.33 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 26.8, 48.25, 50.3, 53.8, 107.1, 107.7, 121.3, 126.2, 126.85, 127.3, 128.0, 128.3, 128.7, 138.4. Anal. calcd for $C_{20}H_{22}N_2$: C, 82.76; H, 7.59. Found: C, 83.15H, 7.56.

3.1.3. 1-Benzyl-2-[2-(benzylamino)ethyl]-5-methylpyrrole (7b). NBS (1.78 g, 10 mmol) was added in three portions to an ice-cold solution of cyclopropanol **3**[8e] (1.28 g, 10 mmol) in CCl_4 (25 mL). After stirring for 1 h the precipitate was filtered off, and the filtrate was evaporated in vacuo to give 2 g of the crude β-bromoketone **4b** as a yellowish liquid (100%). Owing to the lability of this compound, it was used further without purification. Benzylamine (3.33 mL, 30 mmol) was added to a solution of β-bromoketone **4b** in Et_2O (25 mL). The reaction

mixture was stirred at room temperature for 2 h and evaporated in vacuo. Column chromatography of the residue on alumina (EtOAc–cyclohexane, 1:1) led to 2.74 g (90%) of aminoethylpyrrole **7b** as a yellowish oil. IR ($CHCl_3$): ν_{max} 3327 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.77 (bs, 1H), 2.14 (s, 3H), 2.62–2.84 (m, 4H), 3.68 (s, 2H), 5.02 (s, 2H), 5.84–5.88 (m, 2H), 6.76–6.92 (m, 2H), 7.14–7.36 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 12.2, 26.7, 46.4, 48.2, 53.6, 105.2, 105.6, 125.3, 126.7, 126.8, 127.9, 128.1, 128.2, 128.5, 129.8, 138.4, 140.1. Anal. calcd for $C_{21}H_{24}N_2$: C, 82.84; H, 7.96. Found: C, 82.70; H, 7.78.

3.1.4. 1,5-Dimethyl-2-[2-(methylamino)ethyl]pyrrole (7c). Through a solution of the crude β-bromoketone **4b** (2.1 g, 10 mmol), in benzene (25 mL) methylamine (5–7 equiv.) was bubbled during 15 min. The reaction mixture was stirred at room temperature for 8 h and evaporated in vacuo. The aminoethylpyrrole **7c** was isolated as a yellowish oil by column chromatography on alumina (EtOAc–cyclohexane, 1:1). Yield: 0.99 g (65%). IR ($CHCl_3$): ν_{max} 3360 cm^{-1}. ^1H NMR (400 MHz, CCl_4): δ 2.11 (bs, 1H); 2.25 (s, 3H); 2.50 (s, 3H); 2.72–2.90 (m, 4H); 3.45 (s, 3H); 5.78–5.92 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 12.3, 26.9, 29.9, 36.1, 50.7, 104.4, 104.8, 128.1, 128.6. Anal. calcd for $C_9H_{16}N_2$: C, 70.99; H, 10.61. Found: C, 71.07; H, 10.44.

3.1.5. 6,6-Diethoxy-1-hexen-3-one (8a). Bromine-pyridine complex (1.5 g, 6.3 mmol) was added portionwise over 20 min to a stirred solution of cyclopropanol **2a** (1.18 g, 6.3 mmol) in dry Et_2O (20 mL) at 10°C. The precipitate was removed by filtration, and triethylamine (0.92 mL, 6.6 mmol) was added dropwise to the filtrate. After stirring for 3 h at room temperature followed by filtration of the precipitate, the reaction mixture was evaporated in vacuo. The crude product was purified by column chromatography on silica gel (Et_2O–petroleum ether, 35:65) to give 0.97 g (83%) of compound **8a** as a colorless oil. IR ($CHCl_3$): ν_{max} 1673, 1612 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, J=7.2 Hz, 6H), 1.91 (dt, J=7.2, 5.1 Hz, 2H), 2.65 (t, J=7.2 Hz, 2H), 3.45 (dq, J=9.2, 7.2 Hz, 2H), 3.61 (dq, J=9.2, 7.2 Hz, 2H), 4.48 (t, J=5.1 Hz, 1H), 5.79 (dd, J=10.8, 1.5 Hz, 1H), 6.20 (dd, J=17.4, 1.5 Hz, 1H), 6.32 (dd, J=17.4, 10.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 15.2, 27.8, 34.4, 61.6, 102.0, 127.7, 136.5, 200.0. Anal. calcd for $C_{10}H_{18}O_3$: C, 64.52; H, 9.68. Found: C, 64.75; H, 9.66.

3.1.6. 5-(2-Methyl-1,3-dioxolan-2-yl)-1-penten-3-one (8b). NBS (1.78 g, 10 mmol) was added in three portions to an ice-cold solution of cyclopropanol **2b**[8e] (1.72 g, 10 mmol) in CCl_4 (25 mL). After stirring for 1 h followed by filtration of precipitate, the reaction mixture was evaporated in vacuo. The crude β-bromoketone **5b** was dissolved in Et_2O (25 mL) and triethylamine (4.25 mL, 30 mmol) was added. The reaction mixture was refluxed for 1 h, the precipitate was filtered off, the solution was washed with brine (15 mL), dried (Na_2SO_4) and evaporated. The product was purified by distillation in vacuo to give 1.36 g (80%) of ketone **8b** as a colorless liquid. Bp 78–80°C/2 Torr. IR ($CHCl_3$): ν_{max} 1680, 1627 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 1.25 (s, 3H), 2.0 (t, J=7.0 Hz, 2H), 2.60 (t, J=7.0 Hz, 2H), 3.87 (s, 4H), 5.64–6.40 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 23.7, 32.6, 33.9, 64.4, 109.0, 127.5, 136.2, 199.9. Anal. calcd for $C_9H_{14}O_3$: C, 63.50; H, 8.31. Found: C, 63.59; H, 8.26.

3.1.7. 4-Oxo-6-succinimidohexanal (9a). K_2CO_3 (0.07 g, 0.5 mmol) and triethylamine (0.07 mL, 0.5 mmol) were added to a solution of 6,6-diethoxy-1-hexen-3-one **8a** (0.94 g, 5 mmol) and succinimide (0.5 g, 5 mmol) in *i*-PrOH (10 mL). The reaction mixture was refluxed for 1 h, cooled to room temperature and evaporated in vacuo. The residue was dissolved in Et_2O (15 mL), washed with water (2×3 mL) and brine (3 mL), and dried over Na_2SO_4. The solvent was removed in vacuo, the residue was dissolved in acetone (10 mL) and cation exchange resin in H^+-form (0.3 g) was added to the solution. After stirring for 2 h the cation exchange resin was removed by filtration and the solvent was evaporated. The residue was purified by recrystallisation from *i*-PrOH to give 0.85 g (80%) of aldehyde **9a** as white needles. Mp 85°C. IR ($CHCl_3$): ν_{max} 1689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.72 (bs, 4H), 2.74- 2.79 (m, 4H), 2.84 (t, J=7.2 Hz, 2H), 3.81 (t, J=7.2 Hz, 2H), 9.76 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 28.1, 33.8, 34.6, 37.4, 39.6, 176.9, 200.0, 205.7. Anal. calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.16. Found: C, 57.11; H, 6.14.

3.1.8. 7-Succinimido-2,5-heptanedione (9b). K_2CO_3 (0.1 g, 0.7 mmol) and triethylamine (0.1 mL, 0.72 mmol) were added to a solution of ketone **8b** (1.7 g, 10 mmol) and succinimide (0.99 g, 10 mmol) in *i*-PrOH (20 mL). The reaction mixture was refluxed for 1 h. The volatile compounds were removed in vacuo, water (20 mL) was added to the residue, and the mixture was extracted with dichloromethane (3×15 mL). The organic phase was washed with brine (15 mL), dried over Na_2SO_4 and evaporated. To the residue was added acetone (10 mL), CH_2Cl_2 (20 mL) and *p*-toluenesulfonic acid (0.02 g, 0.1 mmol), and the mixture was refluxed for 1.5 h. After evaporation of the solvent in vacuo the residue was dissolved in CH_2Cl_2 (20 mL), washed with brine (3×10 mL) and dried over Na_2SO_4. The solvent was removed and the product was recrystallised from *i*-PrOH to give 2.08 g (92%) of compound **9b** as white needles. Mp 65–68°C. IR ($CHCl_3$): ν_{max} 1707 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.62–2.78 (m, 8H), 2.82 (t, J=7.0 Hz, 2H), 3.78 (t, J=7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 28.1, 29.8, 33.8, 36.0, 36.8, 39.6, 176.9, 206.4, 206.8. Anal. calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.73. Found: C, 58.44; H, 6.60.

3.1.9. 1-Benzyl-2-(2-succinimidoethyl)pyrrole (7d). Benzylamine (0.1 mL, 0.9 mmol) was added to a stirred solution of ketoaldehyde **9a** (0.19 g, 0.9 mmol) in methanol (5 mL) at 30°C. The reaction mixture was stirred for 10 min and the solvent was evaporated in vacuo. Column chromatography of the residue on silica gel (Et_2O–petroleum ether; 35:65) gave 0.23 g (91%) of compound **7d** as white crystals. Mp 107°C. IR ($CHCl_3$): ν_{max} 1680 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.64 (bs, 4H), 2.76 (t, J=7.7 Hz, 2H), 3.67 (t, J=7.7 Hz, 2H), 5.12 (s, 2H), 6.01 (m, 1H), 6.11 (dd, J=3.5, 2.8 Hz, 1H), 6.64 (dd, J=2.8, 1.8 Hz, 1H), 7.01–7.03 (m, 2H), 7.23–7.32 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 24.2, 28.0, 38.0, 50.2, 107.2, 107.7, 121.8, 126.3, 127.3, 128.3, 128.6, 138.2, 176.8. Anal. calcd for $C_{17}H_{18}N_2O_2$: C, 72.34; H, 6.38. Found: C, 72.58; H, 6.32.

3.1.10. 1-Benzyl-5-methyl-2-(2-succinimidoethyl)pyrrole (7e). Diketone **9b** (2.25 g, 10 mmol) was dissolved in *i*-PrOH (20 mL) and benzylamine (1.08 mL, 10 mmol) was added. The resulting solution was stirred at room temperature for 2 h. The precipitate was separated by filtration and recrystallised from *i*-PrOH to give 2.56 g (97%) of compound **7e** as white needles. Mp 104–105°C. IR ($CHCl_3$): ν_{max} 1691 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.62 (s, 4H), 2.72 (t, J=8.0 Hz, 2H), 3.63 (t, J=8.0 Hz, 2H), 5.10 (s, 2H), 5.88 (d, J=3.5 Hz, 1H), 5.94 (d, J=3.5 Hz, 1H), 6.84–6.92 (m, 2H), 7.18–7.32 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 12.3, 24.8, 28.1, 38.4, 46.6, 105.9, 106.4, 125.6, 127.0, 127.7, 128.7, 129.0, 138.5, 176.9. Anal. calcd for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.82. Found: C, 72.78; H, 6.76.

3.1.11. 1,5-Dimethyl-2-(2-succinimidoethyl)pyrrole (7f). Dry methylamine (50 mmol) was bubbled through a solution of diketone **9b** (2.25 g, 10 mmol) in *i*-PrOH (20 mL) at 40°C for 15 min. The reaction mixture was stirred at room temperature for 2 h, the precipitate was separated by filtration and recrystallised from *i*-PrOH to give 1.62 g (86%) of compound **7f** as yellowish crystals. Mp 108–110°C. IR ($CHCl_3$): ν_{max} 1680 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.22 (s, 3H), 2.68 (s, 4H), 2.84 (t, J=8.0 Hz, 2H), 3.46 (s, 3H), 3.70 (t, J=8.0 Hz, 2H), 5.76 (d, J=3.0 Hz, 1H), 5.82 (d, J=3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 12.4, 24.9, 28.1, 30.0, 38.0, 105.0, 105.7, 127.3, 129.0, 176.9. Anal. calcd for $C_{12}H_{16}N_2O_2$: C, 65.42; H, 7.34. Found: C, 65.49; H, 7.27.

3.2. General procedure for the synthesis of tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridines 10a–i

Arylcarboxaldehyde (benzaldehyde, 4-chloro-, 4-fluoro-, 3-nitrobenzaldehyde or 2-hydroxy-5-nitrobenzaldehyde) (1.3 mmol) was added to a solution of aminoethylpyrrole **7a–c** (1.3 mmol) in *i*-PrOH (2 mL). The reaction mixture was stirred at 50°C for 15 min and then kept at room temperature overnight. The precipitate was separated by filtration and compounds **10a–e**,**g–i** were recrystallised from *i*-PrOH. Compound **10f** was isolated by column chromatography (EtOAc–cyclohexane, 1:1).

3.2.1. 1,5-Dibenzyl-2-methyl-4-phenyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine (10a). Yield: 80%; colorless solid. Mp 135°C. ^1H NMR (200 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.32–2.74 (m, 3H), 3.00–3.14 (m, 1H), 3.24 (d, J=13.5 Hz, 1H), 3.86 (d, J=13.5 Hz, 1H), 4.46 (s, 1H), 4.94 (s, 2H), 5.34 (s, 1H), 6.84–6.98 (m, 2H), 7.08- 7.54 (m, 13H). ^{13}C NMR ($CDCl_3$): δ 12.0, 22.3, 46.5, 47.9, 58.3, 65.3, 104.6, 119.3, 125.1, 125.8, 126.6, 126.8, 127.0, 127.6, 128.0, 128.1, 128.6, 128.7, 137.9, 138.62, 140.0, 144.7. Anal. calcd for $C_{28}H_{28}N_2$: C, 85.66; H, 7.20. Found: C, 85.42; H, 7.00.

3.2.2. 1,5-Dibenzyl-4-(4-chlorophenyl)-2-methyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine (10b). Yield: 78%; colorless solid. Mp 103–104°C. ^1H NMR (200 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.36–2.74 (m, 3H), 2.98–3.14 (m, 1H), 3.23 (d, J=13.5 Hz, 1H), 3.81 (d, J=13.5 Hz, 1H), 4.44 (s, 1H), 4.96 (s, 2H), 5.36 (s, 1H), 6.84–6.96 (m, 2H), 7.12–7.50 (m, 12H). ^{13}C NMR ($CDCl_3$): 12.0, 22.2, 46.6, 47.8, 58.3, 64.5, 104.5, 118.7, 125.2, 125.8, 126.8, 127.1, 127.8, 128.1, 128.3, 128.6, 128.7, 129.9, 132.4, 138.5, 139.7, 143.4. Anal. calcd for $C_{28}H_{27}N_2Cl$: C, 78.75; H, 6.39. Found: C, 78.93; H, 6.11.

3.2.3. 1,5-Dibenzyl-4-(4-fluorophenyl)-2-methyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine (10c). Yield: 65%; colorless solid. Mp 72°C. ^1H NMR (200 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.36–2.74 (m, 3H), 3.00–3.14 (m, 1H), 3.23 (d, J=13.5 Hz, 1H), 3.81 (d, J=13.5 Hz, 1H), 4.46 (s, 1H), 4.96 (s, 2H), 5.34 (s, 1H), 6.84–7.48 (m, 14H). ^{13}C NMR ($CDCl_3$): 12.0, 22.2, 46.5, 47.9, 58.2, 64.4, 104.5, 114.9 (H*C*=CF, d, J=21 Hz), 119.1, 125.1, 125.7, 126.7, 127.0, 127.7, 128.1, 128.6, 128.7, 130.0 (C_{meta}, d, J=7 Hz), 138.5, 139.9, 140.5 (C_{para}, d, J=2 Hz), 161.8 (*C*F, d, J=244 Hz). Anal. calcd for $C_{28}H_{27}N_2F$: C, 81.91; H, 6.64. Found: C, 81.78; H, 6.42.

3.2.4. 1,5-Dibenzyl-2-methyl-4-(3-nitrophenyl)-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine (10d). Yield: 75%; colorless solid. Mp 58°C. IR ($CHCl_3$): ν_{max} 1530, 1346 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.06 (s, 3H), 2.32–2.72 (m, 3H), 2.96–3.12 (m, 1H), 3.34 (d, J=13.5 Hz, 1H), 3.80 (d, J=13.5 Hz, 1H), 4.60 (s, 1H), 4.98 (s, 2H), 5.36 (s, 1H), 6.91 (d, J=7.5 Hz, 2H), 7.14–7.40 (m, 8H), 7.48 (t, J=7.5 Hz, 1H), 7.80 (d, J=7.5 Hz, 1H), 8.11 (d, J=7.5 Hz, 1H), 8.36 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.0, 21.8, 46.6, 47.4, 58.4, 64.1, 104.4, 117.6, 122.0, 123.5, 125.5, 125.7, 127.0, 127.2, 128.3, 128.6, 128.8, 129.0, 134.7, 138.4, 139.4, 147.5. Anal. calcd for $C_{28}H_{27}N_3O_2$: C, 76.85; H, 6.23. Found: C, 76.60; H, 6.44.

3.2.5. 1,5-Dibenzyl-4-(2-hydroxy-5-nitrophenyl)-2-methyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine (10e). Yield: 63%; yiellowish solid. Mp 120–122°C. IR ($CHCl_3$): ν_{max} 3360 (br), 1597, 1349 cm^1. ^1H NMR (200 MHz, $CDCl_3$): δ 2.06 (s, 3H), 2.34–2.72 (m, 3H), 3.06–3.24 (m, 1H), 3.45 (d, J=13.0 Hz, 1H), 4.03 (d, J=13.0 Hz, 1H), 4.80 (s, 1H), 4.94 (s, 2H), 5.50 (s, 1H), 6.78–7.56 (m, 13H), 14.72 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 12.0, 21.0, 46.4, 46.7, 58.2, 64.6, 104.7, 114.1, 116.9, 124.4, 124.9, 125.2, 125.6, 127.1, 127.3, 127.9, 128.7, 128.8, 129.0, 129.5, 136.2, 138.0, 140.1, 163.7. Anal. calcd for $C_{28}H_{27}N_3O_3$: C, 73.17; H, 5.93. Found: C, 73.33; H, 6.01.

3.2.6. 4-Phenyl-1,2,5-trimethyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine (10f). Yield: 50%; colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.24 (s, 3H), 2.50–2.76 (m, 2H), 2.84–3.04 (m, 1H), 3.10–3.26 (m, 1H), 3.34 (s, 3H), 4.02 (s, 1H), 5.16 (s, 1H), 7.16–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$): δ12.0, 22.8, 29.5, 43.6, 53.2, 68.1, 103.4, 119.2, 124.7, 126.9, 127.5, 128.0, 128.6, 144.2. Anal. calcd for $C_{16}H_{20}N_2$: C, 79.94; H, 8.40. Found: C, 79.76; H, 8.25.

3.2.7. 4-(3-Nitrophenyl)-1,2,5-trimethyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine (10g). Yield: 63%; yellow solid. Mp 120–122°C. IR ($CHCl_3$): ν_{max} 1533, 1353 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.08 (s, 3H), 2.24 (s, 3H), 2.52–2.82 (m, 2H), 2.84–3.04 (m, 1H), 3.10–3.24 (m, 1H), 3.38 (s, 3H), 4.18 (s, 1H), 5.14 (s, 1H), 7.24–9.26 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 12.0, 22.6, 29.6, 43.5, 52.7, 67.2, 103.1, 117.8, 122.0, 123.4, 124.9, 128.0, 128.9,

134.7, 147.2, 148.4. Anal. calcd for $C_{16}H_{19}N_3O_2$: C, 67.33; H, 6.72. Found: C, 67.58; H, 6.54.

3.2.8. 1,5-Dibenzyl-4-phenyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine (10h). Yield: 77%; colorless solid. Mp 117°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.36–2.74 (m, 3H); 3.00–3.12 (m, 1H); 3.23 (d, J=13.5 Hz, 1H); 3.85 (d, J=13.5 Hz, 1H); 4.48 (s, 1H); 4.92 (s, 2H); 5.57 (d, J=2.5 Hz, 1H); 6.49 (d, J=2.5 Hz, 1H); 6.96–7.50 (m, 15H). ^{13}C NMR ($CDCl_3$): δ 22.4, 48.1, 50.3, 58.6, 65.7, 106.3, 120.4, 121.1, 126.3, 126.9, 127.0, 127.2, 127.6, 128.4, 128.5, 128.9, 129.0, 138.7, 140.3, 144.9. Anal. calcd for $C_{27}H_{26}N_2$: C, 85.71; H, 6.88. Found: C, 86.02; H, 6.86.

3.2.9. 1,5-Dibenzyl-4-(4-chlorophenyl)-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine (10i). Yield: 70%; colorless solid. Mp 105°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.36–2.72 (m, 3H), 2.98–3.12 (m, 1H), 3.23 (d, J=14.0 Hz, 1H), 3.81 (d, J=14.0 Hz, 1H), 4.46 (s, 1H), 4.94 (s, 2H), 5.56 (d, J=3.0 Hz, 1H), 6.50 (d, J=3.0 Hz, 1H), 6.96–7.46 (m, 14H). Anal. calcd for $C_{27}H_{25}N_2Cl$: C, 78.55; H, 6.06. Found: C, 78.82; H, 5.88.

3.2.10. 1-Benzyl-2-[2-(5-hydroxy-2-oxopyrrolidino)-ethyl]pyrrole (11a). Sodium borohydride (0.68 g, 17.9 mmol) was added portionwise over 15 min to a solution of succinimidopyrrole **7d** (0.5 g, 1.77 mmol) in a mixture of methanol (6 mL) and THF (2 mL), cooled to −4°C. The reaction mixture was stirred at room temperature overnight and then poured into a vigorously stirred mixture of saturated aqueous $NaHCO_3$ (10 mL) and Et_2O (10 mL), cooled in an ice-water bath. The aqueous layer was separated and extracted with Et_2O (3×3 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated in vacuo to give 0.50 g (100%) hemiaminal **11a** as white crystals. Compound **11a** was used without purification. IR ($CHCl_3$): ν_{max} 3600, 1686 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (bs, 1H), 1.70–1.83 (m, 1H), 2.16–2.28 (m, 2H), 2.45–2.54 (m, 1H), 2.72–2.84 (m, 2H), 3.38–3.46 (m, 2H), 4.83–4.86 (m, 1H), 5.08 (s, 2H), 6.00–6.02 (m, 1H), 6.14 (dd, J=3.5, 2.8 Hz, 1H), 6.67 (dd, J=2.8, 1.8 Hz, 1H), 7.05–7.07 (m, 2H), 7.26–7.33 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 24.7, 28.3, 28.8, 40.4, 50.4, 83.8, 107.1, 107.4, 121.8, 126.4, 127.4, 128.7, 129.9, 138.3, 174.8.

3.2.11. 1-Benzyl-2-[2-(5-hydroxy-2-oxopyrrolidino)-ethyl]-5-methylpyrrole (11b). Sodium borohydride (0.38 g, 10 mmol) was added in one portion to a solution of succinimidopyrrole **7e** (0.30 g, 1 mmol) in a mixture of methanol (8 mL) and THF (2 mL), cooled to −25°C. The reaction mixture was stirred at temperature below −10°C for 1 h and then poured into a vigorously stirred mixture of saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL), cooled in an ice-water bath. The aqueous layer was separated and extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give 0.30 g (100%) of crude hemiaminal **11b** as white crystals which were used without further purification in next step. Mp 120–122°C. IR ($CHCl_3$): ν_{max} 3599, 3320 (br), 1689 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.66–1.86 (m, 2H); 2.18 (s, 3H); 2.18–2.34 (m, 1H); 2.40–2.52 (m, 1H), 2.54–2.68 (m, 1H), 2.68–2.82, (m, 2H); 3.34–3.48 (m, 2H); 4.86–4.98 (m, 1H); 5.06 (s, 2H); 5.86–5.98 (m, 2H); 6.84–6.96 (m, 2H); 7.14–7.28 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 12.3, 25.2, 28.3, 28.8, 40.6, 46.6, 83.8, 105.7, 106.0, 125.6, 127.1, 128.7, 128.9, 129.2, 138.5, 174.7. Anal. calcd for $C_{18}H_{22}N_2O_2$: C, 72.44; H, 7.45. Found: C, 72.16; H, 7.58.

3.2.12. 1,5-Dimethyl-2-[2-(5-hydroxy-2-oxopyrrolidino)-ethyl]pyrrole (11c). The title compound was obtained in quantitative yield from succinimidopyrrole **7f** by a similar way. Mp 132–134°C. IR ($CHCl_3$): ν_{max} 3600, 3300 (br), 1687 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.68–1.98 (m, 2H); 2.16 (s, 3H); 2.14–2.34 (m, 2H); 2.40–2.64 (m, 1H); 2.68–2.94 (m, 2H); 3.40 (s, 3H); 3.46–3.58 (m, 2H); 4.88–5.06 (m, 1H); 5.66–5.88 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 12.4, 25.3, 28.9, 30.1, 31.9, 41.0, 84.3, 105.0, 105.1, 129.0, 129.1, 174.8. Anal. calcd for $C_{12}H_{18}N_2O_2$: C, 64.83; H, 8.18. Found: C, 64.76; H, 8.25.

3.2.13. 3-Benzyl-4,5,7,8,9,9a-hexahydro-3*H*-pyrrolo[2,3-*g*]indolizin-7-one (12a). Silica (1 g) containing 1% of oxalic acid[15] was added to a stirred solution of hemiaminale **11a** (0.5 g) in Et_2O (20 mL). The reaction mixture was stirred for 90 min and then filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (3 mL), brine (3 mL), and then dried over Na_2SO_4. The solution was evaporated in vacuo and the crude product was purified by column chromatography on silica gel (Et_2O) to give 0.4 g (85%) of pyrroloindolizinone **12a** as a colorless oil. IR ($CHCl_3$): ν_{max} 1686 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73–1.84 (m, 1H), 2.39–2.67 (m, 5H), 2.89–2.96 (m, 1H), 4.40 (dd, J=12.0, 5.5 Hz, 1H), 4.69–4.72 (m, 1H), 4.96 (s, 2H), 6.0 (d, J=2.56, 1H), 6.63 (d, J=2.56, 1H), 6.97–7.01 (m, 2H), 7.23–7.32 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 21.6, 27.1, 31.7, 36.5, 50.1, 55.1, 103.1, 119.8, 121.1, 124.7, 126.4, 127.5, 128.7, 137.6, 173.5. Anal. calcd for $C_{17}H_{18}N_2O$: C, 76.69; H, 6.77. Found: C, 76.76; H, 6.76.

3.2.14. 3-Benzyl-2-methyl-4,5,7,8,9,9a-hexahydro-3*H*-pyrrolo[2,3-*g*]indolizin-7-one (12b). To a stirred solution of hemiaminal **11b** (1.19 g, 4 mmol) in CH_2Cl_2 (63 mL), cooled to −20°C (bath temperature), triethylamine (1.67 mL, 12 mmol) and methanesulfonyl chloride (0.46 mL, 6 mmol) were added. The reaction mixture was stirred at room temperature for 15 min and was quenched with saturated aqueous $NaHCO_3$ (100 mL). The aqueous phase was separated, extracted with CH_2Cl_2 (3×70 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (Et_2O) to give 1.0 g (90%) of pyrroloindolizinone **12b** as white crystals. Mp 97–98°C. IR ($CHCl_3$): ν_{max} 1680 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.64–1.86 (m, 1H), 2.16 (s, 3H), 2.38–2.74 (m, 5H), 2.95 (td, J=12.0, 5.5 Hz, 1H), 4.40 (dd, J=12.0, 5.5 Hz, 1H), 4.64–4.78 (m, 1H), 4.96 (s, 2H), 5.78 (s, 1H), 6.82–6.96 (m, 2H), 7.18–7.36 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 12.0, 21.9, 27.4, 31.5, 36.8, 46.7, 55.1, 101.9, 118.6, 125.6, 125.7, 127.3, 128.7, 128.9, 137.9, 173.8. Anal. calcd for $C_{18}H_{20}N_2O$: C, 77.10; H, 7.20. Found: C, 77.17; H, 7.24.

3.2.15. 2,3-Dimethyl-4,5,7,8,9,9a-hexahydro-3*H*-pyrrolo[2,3-*g*]indolizin-7-one (12c). The title compound was obtained from succinimidopyrrole **11c** in 90% yield by

a similar way. Mp 120–121°C. IR ($CHCl_3$): ν_{max} 1687 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.60–1.84 (m, 1H), 2.20 (s, 3H), 2.28–2.84 (m, 5H), 2.96 (td, J=12.0, 5.5 Hz, 1H), 3.38 (s, 3H), 4.49 (dd, J=12.0, 5.5 Hz, 1H), 4.66–4.88 (m, 1H), 5.72 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.4, 21.8, 28.0, 32.8, 33.8, 37.2, 55.1, 101.7, 118.3, 125.7, 129.2, 173.9. Anal. calcd for $C_{12}H_{16}N_2O$: C, 70.54; H, 7.91. Found: C, 70.69; H, 7.87.

3.3. General procedure for the reduction of hexahydro-3*H*-pyrrolo[2,3-*g*]indolizin-7-ones (12a–c) to 4,5,7,8,9,9a-hexahydro[2,3-*g*]indolizines (13)

BH_3 (7 mL of 1.7 M solution in THF, 11.3 mmol) was added dropwise over 20 min to a stirred solution of compounds **12a–c** (1.13 mmol) in dry THF (7 mL) at −20°C, and the mixture was stirred overnight. Methanol (5 mL) and saturated aqueous $NaHCO_3$ (8 mL) were added to the mixture, and the precipitate was filtered off, the filtrate was diluted with Et_2O (40 mL), the organic layer was separated, washed with saturated aqueous $NaHCO_3$ (8 mL), brine (40 mL), and dried over Na_2SO_4. The solution was evaporated in vacuo and the crude product was purified by column chromatography on silica gel (cyclohexane–ether, 99:1) to give crystalline products **13a–c**.

3.3.1. 3-Benzyl-4,5,7,8,9,9a-hexahydro-3*H*-pyrrolo[2,3-*g*]indolizine (13a). Yield: 87%. Mp 96°C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.81–1.95 (m, 2H), 2.10–2.18 (m, 1H), 2.48–2.55 (m, 1H), 2.61–2.72 (m, 2H), 2.91–2.97 (m, 1H), 3.17–3.28 (m, 3H), 4.38 (dd, J=7.5, 4.5 Hz, 1H), 4.98 (s, 2H), 5.95 (d, J=3.0 Hz, 1H), 6.64 (d, J=2.6 Hz, 1H), 6.98 (d, J=7.0 Hz, 2H), 7.25–7.34 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 18.4, 21.8, 31.5, 50.15, 53.3, 57.6, 66.2, 104.7, 117.7, 121.6, 122.5, 126.3, 127.6, 128.8, 137.7. Anal. calcd for $C_{17}H_{20}N_2$: C, 80.95; H, 7.94. Found: C, 81.16; H, 7.92.

3.3.2. 3-Benzyl-2-methyl-4,5,7,8,9,9a-hexahydro-3*H*-pyrrolo[2,3-*g*]indolizine (13b). Yield: 78%. Mp 78–79°C. ^1H NMR (200 MHz, $CDCl_3$): δ 1.80–1.95 (m, 3H), 2.12 (s, 3H), 2.44–2.78 (m, 3H), 2.88–3.02 (m, 1H), 3.10–3.28 (m, 3H), 4.39 (dd, J=7.5, 4.5 Hz, 1H), 4.96 (s, 2H), 5.70 (s, 1H), 6.82–6.94 (m, 2H), 7.18–7.40 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 12.0, 18.6, 21.7, 31.4, 46.5, 53.3, 57.5, 66.1, 103.3, 116.1, 121.6, 125.5, 127.2, 128.7, 129.2, 137.9. Anal. calcd for $C_{18}H_{22}N_2$: C, 81.14; H, 8.34. Found: C, 80.97; H, 8.14.

3.3.3. 2,3-Dimethyl-4,5,7,8,9,9a-hexahydro-3*H*-pyrrolo[2,3-*g*]indolizine (13c). Yield: 65 %. Mp 83–84°C. ^1H NMR (200 MHz, $CDCl_3$): δ 1.80–1.96 (m, 3H), 2.18 (s, 3H), 2.52–2.88 (m, 3H), 2.90–3.08 (m, 1H), 3.12–3.30 (m, 3H), 3.38 (s, 3H), 4.32 (dd, J=7.5, 4.5 Hz, 1H), 5.64 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 12.4, 19.0, 22.1, 31.8, 35.9, 53.8, 57.5, 66.4, 102.9, 116.2, 121.7, 129.5. Anal. calcd for $C_{12}H_{18}N_2$: C, 75.73; H, 9.55. Found: C, 75.88; H, 9.37.

Acknowledgements

The authors are grateful to the Ministry of Education of Belarus and the INTAS program of the European Union.

References

1. Yakhontov, L. N.; Prokopov, A. A. *Russ. Chem. Rev.* **1980**, *49*, 428.
2. Varlamov, A. V.; Borisova, T. N.; Voskressensky, L. G. *Synthesis* **2002**, 155.
3. Esser, F.; Pook, K.-H.; Carpy, A. *Synthesis* **1990**, 72.
4. Decker, M.; Faust, R.; Wedig, M.; Nieger, M.; Holzgrabe, U.; Lehmann, J. *Heterocycles* **2001**, *55*, 1455.
5. Bagutskii, V. V.; Kulinkovich, O. G. *Khim. Geterotsikl. Soedin.* **2000**, 617.
6. (a) Soerens, D.; Sandrin, J.; Undemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Huetchins, L.; Di Pierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 1179. (b) Paulvannan, K.; Hale, R.; Mesis, R.; Chen, T. *Tetrahedron Lett.* **2002**, *43*, 203.
7. Jawdosiuk, M.; Cook, J. M. *J. Org. Chem.* **1984**, *49*, 2699.
8. (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* **1991**, 234. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Pritytskaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244. (c) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I. *Zh. Org. Khim.* **1991**, *27*, 294. (d) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I. *Zh. Org. Khim.* **1991**, *27*, 1428. (e) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Zh. Org. Khim.* **1991**, *27*, 2132.
9. Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Zh. Org. Khim.* **1991**, *27*, 1431.
10. (a) Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 675. (b) Carson, J. R.; Maryanoff, B. E. US Patent, 4, 572, 911, 1986.
11. Spirocompound, **6** was obtained in 95% yield merely by distillation of **2a** in vacuo. Bp 60°C (12 Torr). ^1H NMR (200 MHz, $CDCl_3$): δ 0.42–0.60 (m, 2H), 0.76–0.94 (m, 2H), 1.20 (t, J=7.0 Hz, 3H), 1.86–2.26 (m, 4H), 3.42 (dq, J=9.8, 7.0 Hz, 1H), 3.68 (dq, J=9.8, 7.0 Hz, 1H), 5.14 (dd, J=4.5, 1.5 Hz, 1H).
12. Tanis, S. P.; Deaton, M. V.; Dixon, L. A.; McMills, M. C.; Raggon, J. W.; Collins, M. A. *J. Org. Chem.* **1998**, *63*, 6914.
13. *cf.* Schoemaker, H. E.; Boer-Terpstra, Tj.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 143.
14. Okano, T.; Sakaida, T.; Eguchi, S. *Heterocycles* **1997**, *44*, 227.
15. Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63.